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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,064	07/18/2001	Avi Ashkenazi	10466/115	1672

28457 7590 07/30/2003

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EXAMINER

KEMMERER, ELIZABETH

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

09/909,064

Applicant(s)

ASHKENAZI ET AL.

Examiner

Elizabeth C. Kemmerer, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 39-47, 49-52 and 54-58 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 44-47 and 49-51 is/are allowed.
- 6) ☒ Claim(s) 39-43, 52 and 54-58 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Status of Application, Amendments, And/Or Claims***

The amendment filed 27 May 2003 (Paper No. 10) has been entered in full. Claims 1-38, 48 and 53 are canceled. Claims 39-47, 49-52 and 54-58 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Withdrawn Objections And/Or Rejections***

The issue regarding priority is resolved.

The rejection of claims 39-44, 47, 48 and 52-58 under 35 U.S.C. § 112, second paragraph as set forth at pp. 3-4 of the previous Office Action (Paper No. 8, 25 February 2003) is *withdrawn* in view of the canceled and amended claims, and Applicant's arguments regarding the specification's disclosure of the location of the transmembrane and extracellular domains of the recited protein (Paper No. 10, 27 May 2003).

The rejection of claims 39-44, 47, 48 and 52-58 under 35 U.S.C. § 112, first paragraph, regarding scope of enablement, as set forth at pp. 4-7 of the previous Office Action (Paper No. 8, 25 February 2003) is *withdrawn* upon further consideration. Please see section on 35 U.S.C. § 112, first paragraph, below.

The rejection of claims 39-44, 47, 48, 53 and 55-58 under 35 U.S.C. § 112, first paragraph, regarding inadequate written description, as set forth at pp. 7-10 of the

previous Office Action (Paper No. 8, 25 February 2003) is *withdrawn* in view of the canceled and amended claims (Paper No. 10, 27 May 2003).

**35 U.S.C. § 112, First Paragraph**

Claims 39-43, 52 and 54-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO: 292 or the mature form thereof, which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells, does not reasonably provide enablement for other variants of SEQ ID NO: 292. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant rejection differs from the previous rejection set forth at pp. 4-7 of the previous Office Action (Paper No. 8, 25 February 2003) in the following way.

Previously, it was indicated that pp. 210-211 of the specification disclosed that PRO331 induced an immune/inflammatory response. This section of the specification disclosed the results of PRO331 in EXAMPLE 77, Skin Vascular Permeability Assay (Assay 64). It is noted that the instant claims have been amended to recite that the PRO331 variants possess the activity suggested in the previous Office Action, namely, "capable of inducing an immune or inflammatory response". Upon further consideration, however, it has been determined that Assay 64 does not provide the skilled artisan with

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guidance for how to use the claimed polypeptides. In Assay 64, a sample of purified polypeptide is injected intradermally into the backs of hairless guinea pigs. The resulting blemishes at the injection sites are measured, and the injection sites are subjected to histopathological analysis to detect infiltration of inflammatory cells. Injection sites with visible inflammatory cells (including neutrophilic, eosinophilic, monocytic or lymphocytic cells) are scored positive. However, the skilled artisan would conclude that a positive result in this assay indicates that the polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic. Please see attached Barsoun et al. (1997, *Journal of Antimicrobial Chemotherapy* 40 :721-724) who induce a hypersensitivity response in mice in a similar way to that done in instant Assay 64 (p. 722, "Delayed-type hypersensitivity assay"). In general, it is clear from the reference that such a response is not beneficial to the animal, as it indicates toxicity of the injected compound. Similarly, Szalai et al. (2000, *Journal of Immunology* 164:463-468).describe the Arthus reaction in guinea pigs using essentially the same assay as described in instant Assay 64 (p. 464, "Arthus reactions" and "Histology"). Again, the authors clearly indicate that a positive reaction in the assay indicates that the injected substance is an irritant, or is toxic. Thus, a positive result in instant Assay 64 indicates that the polypeptide should not be administered to a mammal, since it is toxic. This information does not guide the skilled artisan as to how to use the claimed polypeptides.

Furthermore, isolated polynucleotides encoding a polypeptide at least 80% identical to the extracellular domain of PRO331 are not enabled by the specification. It

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is highly unlikely that the extracellular domain alone would test positive in any of the assays described, including the inhibition of VEGF stimulated endothelial cell proliferation and endothelial cell apoptosis assays, since an isolated extracellular domain is missing more than half of the full length or mature protein that was tested in the assays.

Finally, it is noted that claim 52 does not recite any limitations regarding the activity of the encoded polypeptide, and thus is not enabled for reasons of record.

Applicant argues (p. 15, response) that the claims have been amended according to the examiner's suggestion and are thus fully enabled. This has been fully considered but is not found to be persuasive, because it has now been determined that Assay 64 does not guide the skilled artisan as to how to use the claimed polypeptides. Due to the office action's reversal with respect to Assay 64, the instant rejection constitutes a new ground of rejection which was not necessitated by Applicant's amendment. Therefore, the instant office action is non-final.

Claims 52 and 54 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection was set forth at pp. 7-10 of the previous Office Action (Paper No. 8, 25 February 2003).

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Applicant argues (p. 15, response) that the claims have been amended according to the examiner's suggestion and are thus adequately described. This has been fully considered but is not found to be persuasive, because claims 52 and 54 do not recite limitations regarding the activity of the encoded polypeptides.

### **Conclusion**

Claims 44-47 and 49-51 are allowable. Claims 39-43, 52 and 54-58 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



ELIZABETH KEMMERER  
PRIMARY EXAMINER

ECK  
July 25, 2003